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a huge migrant male work force, housed in crowded and desperate male dormitories throughout the country and serviced by a large formal and informal sex trade; (2) high rates of other sexually transmitted diseases which facilitate HIV transmission; (3) traditions of gender inequality; (4) predominant HIV clade C infection, which may be more transmissible; (5) inadequate and ineffective government and societal response. Growing anger and hopelessness has resulted in increasing substance abuse and violence against women and children. In its most aberrant form, gang rape of young girls and children occurs regularly as a result of the widely and dangerously held belief that sex with a virgin will cure AIDS.

The response to the epidemic remains slow, confused, and poorly coordinated, and the government continues to resist the introduction of transmission preventing and life prolonging antiretrovirals. President Thabo Mbeki has persisted in his inexplicable flirtation with the view that HIV does not cause AIDS (a belief that he has acquired from disaffected US AIDS "dissident" scientists). The devastatating force of the epidemic and the public views of the government have resulted in widespread lack of information and confusion about basic facts of HIV and AIDS. These are found even among well-informed South Africans. Even without antiretroviral therapy, there is much that can be done to prevent new infections and also to provide comprehensive care, decrease the complications of HIV disease, and alleviate suffering and stigma.

Responsible, accessible, and accurate information is needed. It is in this spirit that *Staying Alive* has been written and produced. Directed at schoolchildren, it is a dense, colorful, factual account of HIV pathogenesis, transmission, and prevention that is intended for widespread distribution in Southern Africa. It represents a meaningful attempt by scientifically oriented adults in the developed world, with the assistance of African colleagues, to inform and educate children about HIV/AIDS. Confronted with an epidemic of such size and consequence, it is difficult to know where to begin. This volume will be limited in its effect, but is certainly a well intentioned and well executed step in the right direction. It is clear that those with and at risk for HIV need to be provided with accurate information about it at a young age, before sexual maturity and HIV risk occur. The information about HIV pathogenesis in *Staying Alive* is complex, but it is presented in an amusing and accessible fashion. Prevention issues are explicitly depicted, including forthright advocacy for condom use. It remains a sadness, however, that treatment of HIV and AIDS and its complications is only lightly and superficially covered. No doubt this reflects a need to adhere to the government party line about opposition to antiretroviral treatment. However, the dangers of treatment receive almost equal coverage as its benefits, and little is said about prevention and treatment of opportunistic diseases and comprehensive holistic care of people with HIV disease. Even in the absence of antiretroviral therapy, much can be done to alleviate suffering and care for those living with HIV. Indeed, this is occurring at a community level throughout South Africa, and needs wider coverage, advocacy, and representation in books of this kind. The authors advocate HIV counseling and testing, but should know that most people with and at risk for HIV disease will come forward only if care and treatment are made available. Finally, the issue of stigma and the need to treat those with HIV with compassion and love is barely touched upon—only in one concluding brief paragraph. Thus, for all of its useful features, this attractive volume misses an opportunity to provide positive information about those already infected and contribute fully to a more positive and less hopeless attitude about HIV/AIDS. Perhaps when treatment finally becomes available in South Africa, this shift in orientation will form a substantial part of a next edition.

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The Heartbreak of Pharmaceutical Failure

Human Trials: Scientists, Investors and Patients in the Quest for a Cure
By Susan Quinn
Cambridge, MA: Perseus Publishing (2001).
295 pp. $26.00

This book transports the reader into the universe of currently incurable diseases, there to appreciate the lengthy, expensive, and often heart breakingly unsuccessful search for new remedies able to provide desperately needed major clinical improvement.

The leading figure in Quinn's scenario is Harvard neurologist Howard Weiner, whose talents and personality are well described in the book's early chapters. He fights a daily battle against his patients' multiple sclerosis (MS), a disease of clinical "ups and downs" occurring mysteriously over time, but with a course that is essentially downhill, with each remission ending not with a return to the former baseline, but to a less normal status. Quinn points out early on that the same unpredictability that makes MS hard to treat makes it difficult to study.

While there is some genetic predisposition to MS, genetics seems to be a minor player here. The disease occurs most commonly in northern latitudes, is common in Scandinavia and almost nonexistent among African blacks.

Weiner's domain is the Boston Center for Neurological Diseases, established in 1985. It has a staff of 140 employees from 33 different countries.

In the battle against MS, a rodent disease has been used as a model. It is referred to as EAE, which is shorthand for experimental autoimmune encephalomyelitis. Unfortunately, while EAE is curable by a number of chemicals, MS is not.

Weiner believed that success might be achievable by taking advantage of what is called "oral tolerance." This term applies to a phenomenon known to exist for a long time. It consists of systemic hyporesponsiveness to an agent fed prior to immunization. Legend has it that Mithradates, a first century Mediterranean king, drank

the blood of ducks that had been fed a poisonous weed to protect himself against poisoning by his enemies. Today, a potion made from poison oak is available at homeopathic pharmacies to protect against the risk of poison oak.

Encouraged by some early results in animals, Weiner decided to pursue the cure of not only MS but also rheumatoid arthritis, giving by mouth the brain substance myelin to MS patients and collagen-rich cartilage from calf noses to the arthritis patients. As optimism and excitement increased, the search became one capable of attracting venture capital and biotech firms. Quinn's book captures this anticipating atmosphere in a highly readable form, taking in not only Wall Street but the media and academe as well.

The early positive screening results were, sad to say, not substantiated in the chronic clinical trials. Improvement was seen in some patients, but the results did not show a significant advantage of active treatment over placebo. The conclusion was heart breaking and the reader gets caught up in the anticipation as the bad news is reported for each trial.

The process of drug development is slow, expensive, and risky. This book was published before the latest report from the Tufts Center for the Study of Drug Development, a report whose expensive figures were $800,000,000 to bring a new chemical entity to market if we count the "dry holes" as well as the "gushers" and both the out-of-pocket expenses and the "cost of money," i.e., what you could have earned with the money spent if it were invested so as to generate a 11% return. Quinn's book accurately describes the many years spent from discovery to new drug approval, and the fact that even when a developer reaches phase I with a drug, i.e., the first human exposure, only 1 in 4 or 1 in 5 such drugs ever make it to market. Only 30% or so of approved drugs ever earn back the money invested in their development.

An especially fascinating part of the Weiner story is the high rate of improvement after placebo. (Fifty six percent was reported in one trial). Placebo benefit is partially explicable on the basis of optimistic anticipation and partially by spontaneous improvement. One can only guess at the explanation in the trials summarized in this book, but MS patients clearly have good reason for hoping that a new medication that showed promise would help them. (Ditto for the research physicians.)

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Cryptobiosis, Extremophily, and the Nature of Life

Life at the Limits: Organisms in Extreme Environments
By D.A. Wharton
Cambridge: Cambridge University Press (2002).
328 pp. $25.00

Traditionally, living things were distinguished from inanimate objects like rocks by their motility and growth, more than by an ability to reproduce. Emphasis on reproductive continuity arose only in the 17th century when microscopists discovered cells and Leeuwenhoek first saw protozoa and bacteria and considered that even the tiniest animalcules multiply only from like kinds. Henry Power noted that vinegar nematode worms could survive freezing and in the next century Reaumur found that some caterpillars could also. At first this suspended animation, or cryptobiosis, was confused with death and resurrection. But we now know that many nematodes, rotifers, tardigrades, arthropods, and microorganisms can survive freezing and/or drying, as can many seeds and fungal or other spores.

I used to tell my students that the ability of brine shrimp (*Artemia*) cysts to survive freezing close to absolute zero means that all the information for a living organism is structural—physically embodied in the structure and three-dimensional arrangement of our constituent molecules. Molecular motion is needed only during growth and function and is therefore less fundamental than structure. Wharton is an expert in animal cryptobiosis, which he accurately expounds here for the general public. But his canvas is much broader, encompassing microorganisms and plants also, which obey the same general principles.

Cyptobiosis tells us that life has two potential states. The animated state allows metabolism, growth, and reproduction and depends on diffusion and molecular collisions in liquid water and liquid lipid membranes; energy must continually be expended to maintain ion gradients and small molecule concentrations within the range compatible with life. During cryptobiosis, dryness and/or freezing prevent diffusion, so that the potential for animate life can be preserved as structure without energy expenditure.

Many organisms cannot enter the cryptobiotic state, for freezing or drying irreversibly disrupts their membranes, allowing small molecules to leak out or in, or lethally denatures their proteins. Only those with evolved adaptations can do so. These involve altering intrinsic protein or membrane lipid structure plus special adaptations, such as proteins that bind to ice crystals to prevent their growth or proteins that actively nucleate ice growth outside cells, where it is less damaging than inside. Some organisms that inhabit low temperatures avoid freezing by making glycoproteins that reduce their freezing temperature (e.g. arctic and antarctic fish) or concentrated polyol or sugar antifreezes (many temperate plants and insects).

A radically different way of coping with extreme conditions is extremophily, the ability to grow and multiply in extremes of temperature or pH or in concentrated salt or ionizing radiation. In contrast to cryptobiotes, which suspend animation in extremis but typically grow best in normal environments, extremophiles grow best under their favored extreme conditions and typically cannot under normal ones. This is because the fluidity of their membranes and the stability of their proteins are specifically adapted to their preferred extremes. Well-known examples are thermophilic, psychrophilic, acidophilic, and halophilic bacteria.

Wharton refers to extremophiles as showing capacity